2- (2-AMINO-1,6-DIHYDRO-6-OXO-PURIN-9-YL) METHOXY-1,3- PROPANEDIOL DERIVATIVE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of app. Ser. No. 08/453,223, abandoned filed May 30, 1995; which is in turn a continuation-in-part of app. Ser. No. 08/281,893, filed Jul. 28, 1994, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel antiviral drug, particularly an amino acid ester of a purine derivative, and most particularly to an ester derived from ganciclovir and L-valine and pharmaceutically acceptable salts thereof. The invention also relates to intermediate compounds, synthetic methods for making the antiviral drug, and to methods of antiviral and related disease treatment, and pharmaceutical compositions therefor.

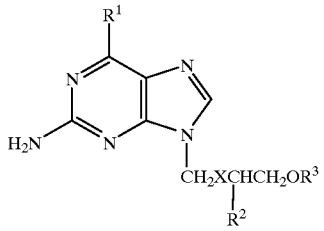
More specifically, the invention relates to the L-monovaline ester derived from 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol and its pharmaceutically acceptable salts.

2. Background Information

British Patent 1523865 describes antiviral purine derivatives with an acyclic chain in the 9-position. Among those derivatives 2-(2-amino-1,6-dihydro-6-oxo-1,6-dihydro-purin-9-yl)methoxy-ethanol with the INN name acyclovir has been found to have good activity against herpes viruses such as herpes simplex. While acyclovir has been found to be very effective upon topical or parenteral administration, it is only moderately absorbed upon oral administration.

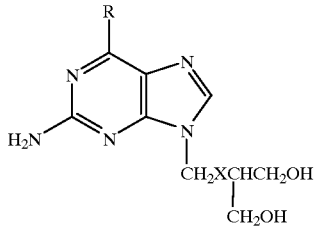
U.S. Pat. No. 4,355,032 discloses the compound 9-[(2-hydroxy-1-hydroxymethyl-ethoxy)methyl]-guanine or 2-(2-amino-1,6-dihydro-6-oxo-purin-9-yl)methoxy-1,3-propanediol with the INN name ganciclovir. Ganciclovir is highly efficacious against viruses of the herpes family, for example, against herpes simplex and cytomegalovirus. It has a relatively low rate of absorption when administered orally and must be used at high dosages when administered by that route. Ganciclovir is most commonly administered via intravenous infusion. This mode of administration has the disadvantage of being very inconvenient to the patient, often requiring the services of a doctor, nurse or other health care professional. There is also a certain risk of infection which is particularly problematic for immunocompromised patients who receive treatment with ganciclovir and may have little resistance against infections. Therefore it has been highly desirable to provide ganciclovir with an improved oral absorption profile.

British Patent Application GB 2 122 618 discloses derivatives of 9-(2-hydroxyethoxymethyl)guanine of the generic formula



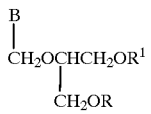
wherein X represents an oxygen or sulphur atom, R^1 represents a hydroxy or an amino group, R^2 represents a hydrogen atom or a group of the formula $—CH_2OR^3{}_a$ and R^3 and $R^3{}_a$ may be the same or different, each represents an amino acid acyl radical and physiologically acceptable salts thereof. These compounds are useful for the treatment of viral infections and have high water solubility which renders them of value in the formulation of aqueous pharmaceutical preparations. While the generic formula in the British patent application includes compounds in which R^2 is the group $—CH_2OR^3{}_a$, specific compounds of this group are not disclosed. The patent application also discloses that formulations used with these compounds with improved water-solubility include oral, rectal, nasal, topical, vaginal or parenteral formulations.

British Patent Application GB 2 104 070 A discloses antiviral compounds of the formula



wherein R is a hydroxy or amino group and X is an oxygen or sulphur atom and physiologically acceptable salts and esters. The general formula includes ganciclovir and physiologically acceptable salts and esters. The esters include those containing a formyloxy group, C_{1-16} (for example, C_{1-6}) alkanoyloxy (e.g. acetoxy or propionyloxy), optionally substituted aralkanoyloxy (e.g. phenyl-C_{1-4} alkanoyloxy such as phenylacetoxy) or optionally substituted aroyloxy (e.g. benzoyloxy or naphthoyloxy) ester grouping at one or both of the terminal positions of the 9-side chain of the compounds of the general formula. The above-mentioned aralkanoyloxy or aroyloxy ester groups may be substituted, for example by one or more halogen (e.g. chlorine or bromo atoms) or amino, nitrile or sulphamido groups, the aryl moiety of the grouping advantageously containing 6 to 10 carbon atoms.

European Patent Application EP 0 375 329 discloses prodrug compounds with the following formula



wherein R and R^1 are independently selected from a hydrogen atom and an amino acyl residue providing at least one